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Activities of NXL104 Combinations with Ceftazidime and Aztreonam against Carbapenemase-Producing *Enterobacteriaceae*▽

David M. Livermore,* Shazad Mushtaq, Marina Warner, Jiancheng Zhang, Sunil Maharjan, Michel Doumith, and Neil Woodford

Antibiotic Resistance Monitoring & Reference Laboratory, HPA Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, United Kingdom

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Combinations of NXL104 with ceftazidime and aztreonam were tested against carbapenem-resistant members of the *Enterobacteriaceae*. Ceftazidime-NXL104 was active against strains with the OXA-48 enzyme or with combinations of impermeability and an extended-spectrum β-lactamase (ESBL) or AmpC enzyme and also against most *Klebsiella* spp. with the KPC enzyme, but metallo-β-lactamase producers were resistant. Aztreonam-NXL104 was active against all carbapenemase producers at 4 and 4 μg/ml, including those with metallo-β-lactamases.

Carbapenems are the preferred treatment for severe infections due to multiresistant members of the *Enterobacteriaceae*, including those with extended-spectrum β-lactamases (ESBLs) or copious AmpC. Carbapenemase-producing *Enterobacteriaceae* remained extremely rare for around 20 years after imipenem's launch in 1985 (11), though there was concern that resistance, particularly to ertapenem, could arise via porin loss in strains with extended-spectrum or AmpC β-lactamase (19).

More recently, carbapenemases have begun to accumulate in the *Enterobacteriaceae*. In particular, clonal *Klebsiella pneumoniae* strains with KPC (class A) carbapenemases have spread widely in the United States, Israel, and latterly Greece (8, 16). Meanwhile, plasmids coding VIM metallo-carbapenemases have disseminated among *K. pneumoniae* strains in Greece (18) and, to a lesser degree, elsewhere in southern Europe, and those coding NDM metallo-enzyme have become distributed among enterobacterial species in the Indian subcontinent (9). OXA (class D) carbapenemases are most important in *Acinetobacter* spp., but OXA-48 is widespread in *K. pneumoniae* in Turkey and is an emerging problem elsewhere (2). International travel and migration are facilitating the dissemination of these enzymes. The United Kingdom, for example, sees the repeated import of strains with VIM and KPC enzymes via patients previously hospitalized in Greece, Cyprus, and Israel and of NDM enzymes via those who have a history of travel and hospitalization in the Indian subcontinent (9).

This diversity presents a considerable challenge, which might best be overcome with β-lactamase inhibitor combinations (5). We examined the ability of NXL104 (1, 22), a novel-structure inhibitor, to protect against carbapenemases when tested with ceftazidime (this combination is currently in phase II trials) and aztreonam, which has the advantage over ceftazidime of stability to metallo-β-lactamases. A smaller study on ceftaroline-NXL104—also under clinical development—was published previously (15).

Clinical isolates with carbapenemases were recent submissions to the Health Protection Agency's Antibiotic Resistance Monitoring and Reference Laboratory, mostly from United Kingdom hospitals. The Reference Laboratory encourages United Kingdom diagnostic microbiology laboratories to submit all members of the *Enterobacteriaceae* that appear to be resistant to carbapenems for further investigation, and the basic characterization of many of the isolates included here has been described (4, 6, 9, 22). There is some overlap of the collections with those of a previously published study (10); however, the numbers of isolates and enzymes studied here were substantially greater, and the investigation included aztreonam-NXL104, which was not studied previously. Carbapenemase genes were identified by PCR (22) and in some cases sequencing. Isolates with bla_{NDM} were examined for the bla_{AmpC} and $bla_{CTX\text{-}M}$ genes, again by PCR (20, 21). Porin lesions were characterized as described previously (4). Identification was done by using the API20E system.

NXL104 was from Novexel, Romainville, France, meropenem from AstraZeneca, Macclesfield, United Kingdom, clavulanate from GlaxoSmithKline, Wembley, United Kingdom, and both piperacillin and tazobactam from Wyeth, Taplow, United Kingdom. Other antibiotics, including ceftazidime and aztreonam, were purchased from Sigma, Poole, United Kingdom. MICs were determined by the CLSI agar dilution method (3), with NXL104, tazobactam, and clavulanate, all used at a fixed concentration of 4 μg/ml. Transconjugants and transformants of *Escherichia coli* with carbapenemase-encoding plasmids were prepared as described previously (14). The *E. coli* DH5α transformant with $bla_{NDM\text{-}1}$ cloned in pUC19 was obtained from screening a genomic library generated by cloning genomic DNA fragments from a *K. pneumoniae* isolate that produced the carbapenemase. The DNA was partially digested with AluI and cloned into the SmaI site of the vector.

Carbapenem MICs for the 65 organisms with carbapenemases (i.e., excluding those with combinations of impermeability and an ESBL or AmpC enzyme) ranged upwards from

* Corresponding author. Mailing address: Antibiotic Resistance Monitoring & Reference Laboratory. HPA Centre for Infections, 61 Colindale Ave., London NW9 5EQ, United Kingdom. Phone: 44-(0)20-8327-7223. Fax: 44-(0)20-8327-6264; E-mail: david.livermore@hpa.org.uk.

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TABLE 1. MIC distributions for carbapenemase-producing isolates and those with a combination of AmpC or ESBL and impermeability[a]

Enzyme and characteristic of isolate(s) (n^b [description])	Drug(s)	No. of isolates for which MIC (μg/ml) is:														
		≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512
KPC (10 [7 *K. pneumoniae* + 3 *Enterobacter* spp.])	Ceftazidime															10*
	Ceftazidime + NXL104			1		3	3			1		2				
	Ceftazidime + clav											2	8*			
	Aztreonam													10*		
	Aztreonam + NXL104		2	3	2	1		1	1							
	Piperacillin														10*	
	Piperacillin + tazobactam												1		9*	
	Imipenem									1	1	3	2	2	1*	
	Meropenem										1	3	1	3	2*	
	Ertapenem												3	2	5*	
SME-1 (1 [*S. marcescens*])	Ceftazidime				1											
	Ceftazidime + NXL104				1											
	Ceftazidime + clav				1											
	Aztreonam										1					
	Aztreonam + NXL104				1											
	Piperacillin												1			
	Piperacillin + tazobactam								1							
	Imipenem														1*	
	Meropenem									1						
	Ertapenem									1						
OXA-48 (19 [all *K. pneumoniae*])	Ceftazidime			1**		8	2					1		2		5
	Ceftazidime + NXL104		1**	1	8	6	3									
	Ceftazidime + clav					1	3	2	6	2	2		3*			
	Aztreonam		1	2	7	1								2	6*	
	Aztreonam + NXL104	1**	4	10	2	2										
	Piperacillin														19*	
	Piperacillin + tazobactam												1		18*	
	Imipenem				1		1	2	4	2		2	3	2	2*	
	Meropenem		1			1	2	2	3			5	1	4		
	Ertapenem				1			1	1	5	1		3	3	4*	
IMP (13 [7 *K. pneumoniae*, 5 *Enterobacter* spp. and 1 *E. coli*])	Ceftazidime														1	12
	Ceftazidime + NXL104	1**														12
	Ceftazidime + clav												13*			
	Aztreonam			2	5	1				1					4*	
	Aztreonam + NXL104		2	3	2	3		1	1							
	Piperacillin											1		1	11*	
	Piperacillin + tazobactam										1		1		11*	
	Imipenem							1	1	2	7	1			1*	
	Meropenem								2		2	8	1			
	Ertapenem									2	2	8			1*	
VIM (5 [4 *K. pneumoniae* and 1 *Enterobacter* sp.])	Ceftazidime												1			4
	Ceftazidime + NXL104												1		1	3
	Ceftazidime + clav												5*			
	Aztreonam				1		1							1	2*	
	Aztreonam + NXL104			2	2	1										
	Piperacillin														5*	
	Piperacillin + tazobactam														5*	
	Imipenem								1		2		2			
	Meropenem						1		1			1		1	1*	
	Ertapenem								2			2			1	
NDM-1 (17 [6 *K. pneumoniae*, 6 *E. coli*, 2 *Enterobacter* spp., 2 *Citrobacter freundii* and 1 *Morganella morganii*])	Ceftazidime															17
	Ceftazidime + NXL104															17
	Ceftazidime + clav												17*			
	Aztreonam		1	1	1						1			2	11*	
	Aztreonam + NXL104	2**	2	1	4	1	2	3	2							
	Piperacillin														17*	
	Piperacillin + tazobactam													1	16*	
	Imipenem									1	1	8	3	2	2*	
	Meropenem								1			7	3	3	3*	
	Ertapenem								1			3	3	5	5*	

Continued on following page

TABLE 1—*Continued*

Enzyme and characteristic of isolate(s) (n^b [description])	Drug(s)	No. of isolates for which MIC (μg/ml) is:														
		≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512
Porin loss and AmpC (5 [all *Enterobacter* spp.])	Ceftazidime												1		4	
	Ceftazidime + NXL104				1	1	3									
	Ceftazidime + clav												5*			
	Aztreonam												3	1	1*	
	Aztreonam + NXL104				1	1	3									
	Piperacillin												1	1	3*	
	Piperacillin + tazobactam										1		2		2*	
	Imipenem							1	1	3						
	Meropenem							2	2	1						
	Ertapenem									1	1	2	1			
Porin loss and ESBL (10 [all *K. pneumoniae*])	Ceftazidime										1				4	5
	Ceftazidime + NXL104					2	7	1								
	Ceftazidime + clav						1			2	1	1	4*			
	Aztreonam												2		8*	
	Aztreonam + NXL104		1		7	1	1									
	Piperacillin														10*	
	Piperacillin + tazobactam														10*	
	Imipenem					1	2	5	2							
	Meropenem				1				2	4		3				
	Ertapenem						1			1		3	5			

[a] Clav, clavulanate. *, MIC ≥ indicated value; **, MIC ≤ indicated value.
[b] *n*, no. of isolates.

0.06 μg/ml, with wide scatters of values for producers of the same enzyme types. Nevertheless, these MICs were >4 μg/ml in 54 cases with imipenem, 51 cases with meropenem, and 59 cases with ertapenem (Table 1). Many of the lowest MICs were for isolates with OXA-48 carbapenemase, though other producers of this enzyme were highly resistant to all three analogues. Isolates with combinations of porin loss and AmpC or ESBL enzymes consistently were more resistant to ertapenem than to other carbapenems, with MICs of >4 μg/ml in 14/15 cases, whereas imipenem and meropenem MICs mostly were 1 to 8 μg/ml, thus straddling the CLSI (3, 3a) and EUCAST (http://www.eucast.org) breakpoints (3).

Eleven of 19 *K. pneumoniae* isolates with the OXA-48 enzyme were susceptible to ceftazidime at ≤1 μg/ml, as was the sole strain with the SME-1 enzyme; the ceftazidime MICs for all other organisms were ≥16 μg/ml. Aztreonam MICs of ≤2 μg/ml were recorded for the same 11/19 OXA-48$^+$ *K. pneumoniae* isolates that were susceptible to ceftazidime and for 8/13, 2/5, and 3/17 isolates with the IMP, VIM, and NDM metallo-carbapenemases, respectively; otherwise, all aztreonam MICs were ≥8 μg/ml and most were >64 μg/ml.

NXL104 reduced the MICs of ceftazidime to ≤2 μg/ml for the following: (i) the eight ceftazidime-resistant isolates with OXA-48 enzymes, (ii) all 15 isolates with combinations of impermeability and ESBLs or AmpC, and (iii) for 7/10 of those with KPC carbapenemases. The remaining 3/10 isolates with KPC enzymes, all of them *Enterobacter* spp., were more resistant, with ceftazidime-NXL104 MICs of 8 to 32 μg/ml. Isoelectric focusing showed that these isolates also copiously produced cloxacillin-inhibited enzymes with a pI of >8.5, which were inferred to be AmpC types. It is likely that these AmpC types, combined with the KPC enzymes, simply overwhelmed the inhibitor. With one exception, the isolates with metallo (IMP, NDM, or VIM) enzymes remained equally as resistant (±1 doubling dilution) to ceftazidime plus NXL104 as to ceftazidime alone. The exception was an *E. coli* isolate with the IMP-1 enzyme, where the ceftazidime MIC fell from 256 μg/ml to 0.03 μg/ml, apparently owing to susceptibility to NXL104 itself at ≤8 μg/ml. In our experience, MICs of NXL104 for *E. coli* are commonly ca. 16 μg/ml whereas those for other members of the *Enterobacteriaceae* are higher (unpublished).

MICs for aztreonam plus NXL104 were ≤4 μg/ml for all the 83 clinical isolates with carbapenemases or combinations of impermeability and AmpC or ESBL and were ≤1 μg/ml for all except 5 *E. coli* isolates with NDM-1 carbapenemase, 2 *Enterobacter* spp. with KPC enzymes, and 1 *E. cloacae* isolate with a combination of porin loss and AmpC.

MICs for *E. coli* J62, DH5α, and JM83/109 transformants and transconjugants with representative class A, B, and D carbapenemases were determined (Table 2). These organisms were less resistant to the carbapenems than the clinical isolates, probably reflecting greater permeability, particularly among the DH5α derivatives. Thus, carbapenem MICs for *E. coli* DH5α and JM109 transformants with the IMP-1, NMC-A, and OXA-48 enzymes all remained at ≤2 μg/ml. KPC-3, IMP-1, and NDM enzymes conferred resistance to ceftazidime in the transconjugants and transformants, whereas the NMC-A and OXA-48 enzymes had little or no effect. Ceftazidime resistance mediated by the KPC-3 enzyme was reversed by NXL104, with the MIC reduced from 64 to 0.25 μg/ml, whereas that mediated by the IMP and NDM enzymes was little affected. The KPC-3 and NMC-A enzymes conferred resistance to aztreonam that was reversed by NXL104, with MICs reduced from >128 to 0.06 μg/ml and from 16 to 0.03 μg/ml, respectively. The OXA-48, IMP-1, and NDM-1 (as expressed by the cloned gene in pUC19) enzymes had a minimal effect on the MICs of aztreonam. Resistance to aztreonam was seen, however, in the transformant with a native plasmid that

TABLE 2. MICs for *E. coli* transconjugants and transformants with carbapenemases

Carbapenemase class or strain	MIC (μg/ml) of drug										
	Ceftazidime	Ceftazidime-NXL104	Ceftazidime-clavulanate	Aztreonam	Aztreonam-NXL104	Cefotaxime	Piperacillin	Piperacillin-tazobactam	Imipenem	Meropenem	Ertapenem
Class A											
J62 KPC-3	64	0.25	32	>128	0.06	128	>128	>128	8	8	8
JM109 NMCA	0.25	≤0.06	0.125	16	≤0.03	≤0.125	32	2	2	1	2
Class B											
DH5α IMP-1	16	4	16	≤0.03	≤0.03	4	2	1	0.5	0.125	0.125
DH5α NDM[a]	>256	>256	>32	8	0.125	128	128	128	8	4	8
DH5α NDM (cloned pUC19)	>256	>256	>32	0.06	≤0.03	256	>128	>128	32	16	16
Class D											
DH5α OXA-48	≤0.125	≤0.060	0.125	≤0.030	≤0.030	0.25	128	32	2	0.125	0.5
Recipients											
DH5α	≤0.125	≤0.06	≤0.06	≤0.03	≤0.03	≤0.125	1	1	0.125	≤0.03	≤0.03
J62	≤0.125	≤0.06	0.125	≤0.03	≤0.03	≤0.125	2	2	0.125	≤0.03	≤0.03
JM83	≤0.125	0.125	0.125	0.06	0.06	≤0.125	2	2	0.25	≤0.03	≤0.03

[a] Also produced CIT-type AmpC β−lactamase.

determined both NDM carbapenemase and a CIT-type AmpC enzyme and was reversed by the presence of NXL104.

Carbapenemase-producing members of the *Enterobacteriaceae* challenge the pharmaceutical chemist and the clinician. Producers are increasing prevalent and are commonly resistant to multiple antibiotic classes; in addition, their enzymes are diverse, including representatives of β-lactamase classes A, B, and D (13). From a U.S. perspective, it is easy to perceive KPC carbapenemases as the main emerging problem, but the VIM and NDM metallo-carbapenemases are most frequent among the *Enterobacteriaceae* in southern Europe (12, 18) and India (9), respectively, whereas OXA-48 is widespread in Turkey (2). All of these enzymes are being disseminated internationally by human travel and migration, and it would be a brave person who wagered which will be dominant in another 3 to 4 years, when cephalosporin-NXL104 combinations potentially may reach the market.

We showed previously that NXL104 at 1 to 4 μg/ml could overcome ceftaroline resistance mediated by the OXA-48 and KPC carbapenemases though not that mediated by metallo-enzymes (10, 15). The present data show that NXL104 can restore the activity of ceftazidime against *K. pneumoniae* with KPC carbapenemase, though resistance remained in some *Enterobacter* sp. isolates with this enzyme, probably because these organisms were also impermeable and had copious AmpC, overwhelming the inhibitor. This limitation is of limited likely impact because KPC enzymes are far more prevalent in *K. pneumoniae* than *Enterobacter* spp. (16). The OXA-48 enzyme did not confer resistance to ceftazidime, so no synergy arose unless other NXL104-inhibited ceftazidime-hydrolyzing enzymes were present; this is in contrast to the behavior seen with ceftaroline, where OXA-48 did confer resistance, overcome by NXL104 (15).

If KPC or OXA-48 are the predominant carbapenemases of the future, then either ceftazidime-NXL104 or ceftaroline-NXL104 should prove an effective answer. These combinations should also be effective against isolates with a carbapenem resistance contingent with combinations of AmpC or ESBL and impermeability, though these have shown little ability to spread in clinical settings and are a lesser concern. The problem arises if metallo-carbapenemases become dominant, since NXL104 cannot inhibit these enzymes, and nor can any other inhibitor in advanced development. One answer is to use a monobactam as the partner drug, since these are stable to metallo-carbapenemases (17), and to protect it against coproduced ESBLs or AmpC enzymes using NXL104 or another inhibitor. The present study has illustrated the potential of this approach, with MICs of aztreonam-NXL104 found to be ≤4 μg/ml against all carbapenemase producers, including those with metallo-enzymes, and ≤1 μg/ml for the huge majority, the exceptions mostly being *E. coli* isolates with the NDM-1 enzyme. The activity of aztreonam-NXL104 against *K. pneumoniae* with KPC carbapenemases was also noted by Endimiani et al (7), who, as in the present study, found MICs consistently lower than those of ceftazidime-NXL104.

REFERENCES

1. **Bassetti, M., E. Righi, and C. Viscoli.** 2008. Novel β-lactam antibiotics and inhibitor combinations. Expert Opin. Invest. Drugs **17:**285–296.
2. **Carrer, A., L. Poirel, M. Yilmaz, O. A. Akan, C. Feriha, G. Cuzon, G. Matar, P. Honderlick, and P. Nordmann.** 2010. Spread of OXA-48-encoding plasmid in Turkey and beyond. Antimicrob. Agents Chemother. **54:**1369–1373.
3. **Clinical and Laboratory Standards Institute.** 2009. Methods for dilution antimicrobial testing of bacteria that grow aerobically, 7th ed., approved standard M7-A7. 2009. Clinical and Laboratory Standards Institute, Wayne, PA.

3a. **Clinical and Laboratory Standards Institute.** 2010. Performance standards for antimicrobial susceptibility testing: 20th informational supplement, M100-S20. Clinical and Laboratory Standards Institute, Wayne, PA.

4. **Doumith, M., M. J. Ellington, D. M. Livermore, and N. Woodford.** 2009. Molecular mechanisms disrupting porin expression in ertapenem-resistant *Klebsiella* and *Enterobacter* spp. clinical isolates from the UK. J. Antimicrob. Chemother. **63:**659–667.
5. **Drawz, S. M., and R. A. Bonomo.** 2010. Three decades of β-lactamase inhibitors. Clin. Microbiol. Rev. **23:**160–201.
6. **Ellington, M. J., J. Kistler, D. M. Livermore, and N. Woodford.** 2007. Multiplex PCR for rapid detection of genes encoding acquired metallo-β-lactamases. J. Antimicrob. Chemother. **59:**321–322.
7. **Endimiani, A., Y. Choudhary, and R. A. Bonomo.** 2009. In vitro activity of NXL104 in combination with β-lactams against *Klebsiella pneumoniae* isolates producing KPC carbapenemases. Antimicrob. Agents Chemother. **53:** 3599–3601.
8. **Kitchel, B., J. K. Rasheed, J. B. Patel, A. Srinivasan, S. Navon-Venezia, Y. Carmeli, A. Brolund, and C. G. Giske.** 2009. Molecular epidemiology of KPC-producing *Klebsiella pneumoniae* isolates in the United States: clonal expansion of multilocus sequence type 258. Antimicrob. Agents Chemother. **53:**3365–3370.
9. **Kumarasamy, K. K., M. A. Toleman, T. R. Walsh, J. Bagaria, F. Butt, R. Balakrishnan, U. Chaudhary, M. Doumith, C. G. Giske, S. Irfan, P. Krish-**

nan, A. V. Kumar, S. Maharjan, S. Mushtaq, T. Noorie, D. L. Paterson, A. Pearson, C. Perry, R. Pike, B. Rao, U. Ray, J. B. Sarma, M. Sharma, E. Sheridan, M. A. Thirunarayan, J. Turton, S. Upadhyay, M. Warner, W. Welfare, D. M. Livermore, and N. Woodford. 2010. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. Lancet Infect. Dis. **10:**597–602.

10. **Livermore, D. M., S. Mushtaq, M. Warner, C. Miossec, and N. Woodford.** 2008. NXL104 combinations versus Enterobacteriaceae with CTX-M extended-spectrum β-lactamases and carbapenemases. J. Antimicrob. Chemother. **62:**1053–1056.
11. **Livermore, D. M., and N. Woodford.** 2006. The β-lactamase threat in *Enterobacteriaceae*, *Pseudomonas* and *Acinetobacter*. Trends Microbiol. **14:**413–420.
12. **March, A., R. Aschbacher, H. Dhanji, D. M. Livermore, A. Bottcher, F. Sleghel, S. Maggi, M. Noale, C. Larcher, and N. Woodford.** 2010. Colonization of residents and staff of a long-term-care facility and adjacent acute-care hospital geriatric unit by multiresistant bacteria. Clin. Microbiol. Infect. **16:**934–944.
13. **Miriagou, V., G. Cornaglia, M. Edelstein, I. Galani, C. G. Giske, M. Gniadkowski, E. Malamou-Lada, L. Martinez-Martinez, F. Navarro, P. Nordmann, L. Peixe, S. Pournaras, G. M. Rossolini, A. Tsakris, A. Vatopoulos, and R. Canton.** 2010. Acquired carbapenemases in gram-negative bacterial pathogens: detection and surveillance issues. Clin. Microbiol. Infect. **16:**112–122.
14. **Mushtaq, S., Y. Ge, and D. M. Livermore.** 2004. Comparative activities of doripenem versus isolates, mutants, and transconjugants of *Enterobacteriaceae* and *Acinetobacter* spp. with characterized β-lactamases. Antimicrob. Agents Chemother. **48:**1313–1319.
15. **Mushtaq, S., M. Warner, G. Williams, I. Critchley, and D. M. Livermore.** 2010. Activity of chequerboard combinations of ceftaroline and NXL104 versus β-lactamase-producing Enterobacteriaceae. J. Antimicrob. Chemother. **65:**1428–1432.
16. **Nordmann, P., G. Cuzon, and T. Naas.** 2009. The real threat of *Klebsiella pneumonia*e carbapenemase-producing bacteria. Lancet Infect. Dis. **9:**228–236.
17. **Queenan, A. M., and K. Bush.** 2007. Carbapenemases: the versatile β-lactamases. Clin. Microbiol. Rev. **20:**440–458.
18. **Vatopoulos, A.** 2008. High rates of metallo-β-lactamase-producing *Klebsiella pneumoniae* in Greece—a review of the current evidence. Euro Surveill. **13:**8203.
19. **Woodford, N., J. W. Dallow, R. L. Hill, M. F. Palepou, R. Pike, M. E. Ward, M. Warner, and D. M. Livermore.** 2007. Ertapenem resistance among *Klebsiella* and *Enterobacter* submitted in the UK to a reference laboratory. Int. J. Antimicrob. Agents **29:**456–459.
20. **Woodford, N., S. Reddy, E. J. Fagan, R. L. Hill, K. L. Hopkins, M. E. Kaufmann, J. Kistler, M. F. Palepou, R. Pike, M. E. Ward, J. Cheesbrough, and D. M. Livermore.** 2007. Wide geographic spread of diverse acquired AmpC β-lactamases among *Escherichia coli* and *Klebsiella* spp. in the UK and Ireland. J. Antimicrob. Chemother. **59:**102–105.
21. **Woodford, N., M. E. Ward, M. E. Kaufmann, J. Turton, E. J. Fagan, D. James, A. P. Johnson, R. Pike, M. Warner, T. Cheasty, A. Pearson, S. Harry, J. B. Leach, A. Loughrey, J. A. Lowes, R. E. Warren, and D. M. Livermore.** 2004. Community and hospital spread of *Escherichia coli* producing CTX-M extended-spectrum β-lactamases in the UK. J. Antimicrob. Chemother. **54:**735–743.
22. **Woodford, N., J. Zhang, M. Warner, M. E. Kaufmann, J. Matos, A. Macdonald, D. Brudney, D. Sompolinsky, S. Navon-Venezia, and D. M. Livermore.** 2008. Arrival of *Klebsiella pneumoniae* producing KPC carbapenemase in the United Kingdom. J. Antimicrob. Chemother. **62:**1261–1264.